REMARKS

I. STATUS OF CLAIMS

Upon entry of the amendments provided herein, claims 1, 3-6, 9-37, 39-42, and 44-77 are pending; claims 1, 3, 5, 16, 20-27, 30, 32-35, 40, 41, 48-51, 56-61, 65, and 72-77 are amended, and claims 2, 7-8, 38 and 43 are herein canceled without prejudice and/or disclaimer.

Amendments to independent claims 1, 30, and 65 are supported by original claim 2. Additional amendments to claims 1, 5, 16, 20-27, 30, 32-35, 40, 41, 48-51, 56-61, 65, and 72-77 are made to correct a minor typographical error in the chemical name of mecamylamine. Specifically, references to N-2,**2**,3-tetramethylbicyclo-[2.1.1]heptan-2-amine have been corrected to recite N-2,**3**,3-tetramethylbicyclo-[2.1.1]heptan-2-amine. That correction would have been obvious to a person of ordinary skill in the art as the Merck Index confirms that the full chemical name of mecamylamine is N-2,**3**,3-tetramethylbicyclo-[2.1.1]heptan-2-amine. Moreover, the correct name is identified in the specification at least in the title of the present invention and at paragraph [012]. It is also noted that submitted herewith is a Substitute Specification under 37 C.F.R. § 1.125(b), which corrects this typographical error in the specification.

Claim 3 is amended to correct the dependency, as claim 2 is now canceled. Accordingly, no new matter is added by those amendments to the claims and their entry is respectfully requested.

II. OBJECTION UNDER 37 C.F.R. § 1.75(c)

The Office maintained the objection to claims 38-51 under 37 C.F.R. § 1.75(c) as being in improper dependent form, i.e., failing to further limit the subject matter of the previous claim. Office Action at page 2. In particular, the Office contends that "[c]laims 39-42 and 44-51 . . . recite an intended use without reciting a specific chemical or physical property of the formulation of claim 30 from which they depend." *Id.* Applicant continues to respectfully disagree with the office's basis for objection for the reasons of record and for the additional reasons provided below.

Based on the Office's rationale, "a specific chemical or physical property of the formulation" must be included in the dependent claims in order for such claims to further limit the subject matter of the previous claim. Office Action at page 2. However, each of claims 39-42 and 44-51 expressly recites a further limitation to the respective claim from which it depends.

For example, as provided in dependent claim 39, it further recites a particular side effect that is minimized with the administration of the modified release formulation of the present invention as claimed in claim 30, in comparison to the administration of a conventional formulation of N-2,3,3-tetramethylbicyclo-[2.1.1]heptan-2-amine, or a pharmaceutically acceptable salt thereof in comparison to the recited a modified-release formulation. Likewise, dependent claims 40 and 41 further define the time period of the maximum plasma concentration; dependent claim 42 further defines the administration period; dependent claims 44 and 45 further define the peak:trough plasma ratio; dependent claims 46 and 47 further define the plasma concentration; and dependent claims 48 and 49 further define the plasma concentration.

As such, Applicant submits that claims 39-42 and 44-57 recite further limitations on a physical property of the formulation of claim 30 from which they all directly or indirectly depend. Thus, Applicant respectfully requests that this objection be withdrawn.

III. REJECTION UNDER 35 U.S.C. § 112, FIRST PARAGRAPH

The Office maintained the rejection of claims 1-29 under 35 U.S.C. § 112, first paragraph, as failing to comply with the written description requirement. Office Action at page 2; Advisory Action. In response to Applicant's arguments, the Office asserts that: (1) there are no working examples; (2) there is no support for minimizing side effects such as heart rate, blurred vision, bladder function or blood pressure; (3) hypothetical situations are only present; and (4) there are no noted conclusions with respect to minimizing and reducing side effects or gastrointestinal motility caused by any pathological condition. *Id.* at page 3. Based on that assertion, the Office concludes that "the skilled artisan in gastroenterology would reasonably require a more detailed description of both disease states characterized by gastrointestinal hypermotility, that are encompassed by the language of claim 1, and of minimization of side effects." *Id.* at page 4. Now, in the Advisory Action, the Office further asserts that "sufficient guidance to support predictable operability, or a reasonable expectation of success, to one of ordinary skill in the art remains absent [from the present application]." Advisory Action. Applicant continues to respectfully disagree and traverses the rejection for the reasons of record and for those found below.

The Office again bases the Section 112, first paragraph, rejection on the lack of working examples and the reliance on hypothetical examples. Office Action at page 3.

As the Office admits at page 3 of the Office Action, the presence or absence of a working example is not the standard by which compliance with Section 112, first paragraph is judged. All that is required is that the specification reasonably convey to one of ordinary skill in the art that as of the filing date of the application, applicant was in possession of the present invention; how the specification shows possession is immaterial. *See In re Kaslow*, 707 F.2d 1366, 1375, 217 U.S.P.Q. 1089, 1096 (Fed. Cir. 1983). Thus, Applicant's lack of actual working examples and reliance on hypothetical examples does not evidence a lack of written description.

A description as filed is presumed to be adequate, unless or until sufficient evidence or reasoning to the contrary has been presented by the examiner to rebut the presumption. M.P.E.P. § 2163 (III)(A) (citing *In re Marzocchi*, 439 F.2d 220, 224, 169 U.S.P.Q. 367, 370 (C.C.P.A. 1970)). As such, the Office has the initial burden of demostrating, by a preponderance of the evidence, why a person of ordinary skill in the art would not recognize in applicant's disclosure a description of the invention defined by the claims. *In re Wertheim*, 541 F.2d 257, 263, 191 U.S.P.Q. 90, 97 (C.C.P.A. 1970). Here, the Office's reasoning for a lack of written description is mere conclusory statements.

The Office misconstrues the written description requirement by not addressing why a more detailed description is necessary for the skilled artisan and instead, merely states that "a more detailed description of both diseases characterized by gastrointestinal hypermotility" and "minimization of side effects" would be required by a skilled artisan. *See* M.P.E.P. § 2163 (III)(A). In fact, the Office's comment that "the specification fails to provide *support* for reducing gastrointestinal [motility]" further

evidences that misunderstanding, as it is not whether *support* for such as a working example is provided, but whether a person of ordinary skill in the art would recognize the applicant's disclosure as a description of the claimed invention. Office Action at page 4 (emphasis added).

Moreover, the Office's contention that "the broad language of the claims encompasses essentially any bowel motility disorder regardless of the etiology of the disease process" again ignores the objective standard for determining written description. Given the amendments provided herein directed to particular gastrointestinal motility disorders, that contention is moot, as the claims now recite specific gastrointestinal motility disorders.

Now, in the Advisory Action, the Office indicates that there is a lack of "sufficient guidance to support predictable operability, or a reasonable expectation of success." The written description standard is not operability or success, as noted above. In fact, the M.P.E.P. expressly states that "[a] general allegation of 'unpredictability in the art' is not sufficient reason to support a rejection for lack of adequate written description." M.P.E.P. § 2163 (III)(A). Here, again, those statements evidence that the Office failed to rebut the presumption that the description is presumed adequate.

In view of the foregoing, Applicant submits that claims 1-29 satisfy the written description requirement under 35 U.S.C. § 112, first paragraph. Accordingly, Applicant respectfully requests the withdrawal of that rejection.

IV. REJECTION UNDER 35 U.S.C. § 103

The Office maintained the rejection of claims 1-77 under 35 U.S.C. § 103(a) as unpatentable over WO 00/35280 to Shytle et al. or WO 00/35279 to Shytle et al. (since both references are related and share a common disclosure, reference herein to "Shytle" encompasses both of the two references). Office Action at page 4. In response to Applicant's arguments, the Office continues to assert that Shytle teaches compositions comprising racemic (both isomers) mecamylamine for the treatment of gastrointestinal motility disorders. *Id.* at page 5. Moreover, the Office contends that "[v]arious dosage forms and dosage ranges, as those presently claimed, are taught by Shytle." *Id.*

Now, in the Advisory Action, the Office further states that "Shytle clearly teaches the administration of mecamylamine for the treatment of spasmogenic intestinal disorders." Applicant continues to respectfully disagree for the reasons of record and to traverse the rejection for the additional reasons provided below.

Shytle recognizes that despite mecamylamine's proven efficacy in the treatment of hypertension, the side effects associated with mecamylamine treatment lead to its "demise as a first line treatment for essential hypertension." Shytle at page 1. For example, the generalized ganglionic blockade with mecamylamine treatment results in atony of the bladder and gastrointestinal tract, impaired sexual function, cycloplegia, xerostomic, diminished perspiration, and postural hypotension. *Id.* According to Shytle, better symptom control and fewer side effects are needed for mecamylamine treatment. *Id.* at page 6. To answer such a need, Shylte provides a composition that includes a therapeutically effective amount of exo-R-mecamylamine or a pharmaceutically

acceptable salt thereof, *substantially free of exo-S-mecamylamine,* in combination with a pharmaceutically acceptable carrier. Shytle at Abstract, 7, and 20-22.

Shytle finds better symptom control by specifically using the R-isomer of mecamyaline for neuropsychiatric disorders. In fact, all the examples provided in Shytle support Shytle's use of mecamyalmine for neuropsychiatric disorders. Example 1 supports that exo-R-mecamylamine was generally more effective at lower doses. Example 2 determines if the enantiomers of mecamylamine differ in their abilities to affect spontaneous locomotor activity. Example 3 determines if the isomers differ in their duration of action blocking the locomotor effects of nicotine. Example 4 tests the effects of mecamylamine enantiomers on haloperidol-induced catalepsy. Example 5 evaluates the effect of exo-R-mecamylamine in blocking nicotine-induced seizures in rats. Example 6 tests exo-R-mecamylamine for its ability to block the stereotypic responde at apomorphine in rats. Example 7 evaluates the effect of exo-R-mecamylamine on nictonic receptors involved in the neuroendocrine response to stress. Example 8 tests the antihypertensive effects of the exo-R-mecamylamine enantiomer by measuring the blockade of the pressor response elicited by sympathetic nerve stimulation in the pithed rat. Example 9 evaluates the efficacy and potency of exo-R-mecamylamine on human α3β4, α4β2, α3β2 and α7 receptors expressed in *Xenopus* oocytes and compared its activity to that of mecamylamine. To that end, there are no examples and no other supporting evidence to treat any type of gastrointestinal condition provided in Shytle.

In order to establish a *prima facie* case of obviousness, Shytle must teach all of the elements of the claims. M.P.E.P. § 2143. Here, Shytle does not even mention the

specific gastrointestinal conditions listed in the present claims, let alone the use of mecamylamine to treat these conditions.

Clearly, the Office is hung-up on claim 62 of Shytle reciting "a method of treating a human spasmogenic intestinal disorders . . . ." However, "[a] prior art reference must be considered in its entirety, i.e., as a whole, including portions that would lead away from the claimed invention." M.P.E.P. § 2141.03(IV) (citing *W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 220 U.S.P.Q. 303 (Fed. Cir. 1983) *cert. denied*, 469 U.S. 851 (1984)) (emphasis original). In violation of this requirement, the Office fails to account for Shytle's *teaching away* from using mecamylamine to treat the specific disorders recited in the present claims.

For example, the Office fails to rectify Shytle's description of the unwanted side effects associated with the administration of mecamylamine that include gastrointestinal side-effects such as atony of the bladder and gastrointestinal tract, dyspepsia, and constipation with claim 62 ("treating . . . spasmogenic intestinal disorders"). Shytle at pages 1, 2, 11, and 12. Moreover, there is no disclosure in Shytle of the specific gastrointestinal conditions recited in the presently amended claims. To that end, the Office fails to correlate the broad "spasmogenic intestinal disorders" with those specific gastrointestinal disorders that arguably, are the adverse side-effects of mecamylamine treatment. The Office has not done so because of the discrepancy between the two teachings, and there is no further guidance from Shytle. Since Shytle did not use "spasmogenic intestinal disorders" to describe some of the side effects such as dyspepsia and constipation and vice-versa, that suggests a difference between the

"spasmogenic intestinal disorders" and the unwanted gastrointestinal side-effects described occurring with mecamylamine treatment.

Accordingly, for at least the above-mentioned reasons, Shytle fails to establish a *prima facie* case of obviousness of any of the pending claims and thus, Applicant respectfully requests the withdrawal of the rejection.

V. CONCLUSION

In view of the foregoing amendments and remarks, Applicant respectfully requests reconsideration of this application and the timely allowance of the pending claims.

Please grant any extensions of time required to enter this response and charge any additional required fees to Deposit Account No. 06-0916.

Respectfully submitted,

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